

## PATENT COOPERATION TREATY

M.H.

PCT

NOTIFICATION OF ELECTION  
(PCT Rule 61.2)Date of mailing (day/month/year)  
17 January 2000 (17.01.00)International application No.  
PCT/GB99/01607International filing date (day/month/year)  
21 May 1999 (21.05.99)

## Applicant

MITRAPHANOUS, Kyriacos, Andreou et al

From the INTERNATIONAL BUREAU

To:

Assistant Commissioner for Patents  
United States Patent and Trademark  
Office  
Box PCT  
Washington, D.C.20231  
ÉTATS-UNIS D'AMÉRIQUE

in its capacity as elected Office

Applicant's or agent's file reference  
P004733WOCTHPriority date (day/month/year)  
22 May 1998 (22.05.98)

1. The designated Office is hereby notified of its election made:

 in the demand filed with the International Preliminary Examining Authority on:  
09 December 1999 (09.12.99) in a notice effecting later election filed with the International Bureau on:  
\_\_\_\_\_2. The election  was was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

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The International Bureau of WIPO  
34, chemin des Colombettes  
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Form PCT/IB/331 (July 1992)

Authorized officer

S. Mafla

Telephone No.: (41-22) 338.83.38

3054629

Copy for the designated Office (DO/US)

PATENT COOPERATION TREATY

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## NOTIFICATION RELATING TO PRIORITY CLAIM

(PCT Rules 26bis.1 and 26bis.2 and  
Administrative Instructions, Sections 402 and 409)

From the INTERNATIONAL BUREAU

To:

HARDING, Charles, Thomas  
D. Young & Co.  
21 New Fetter Lane  
London EC4A 1DA  
ROYAUME-UNIDate of mailing (day/month/year)  
16 August 1999 (16.08.99)Applicant's or agent's file reference  
P004733WOCTHInternational application No.  
PCT/GB99/01607

## IMPORTANT NOTIFICATION

International filing date (day/month/year)  
21 May 1999 (21.05.99)

Applicant

OXFORD BIOMEDICA (UK) LIMITED et al

The applicant is hereby notified of the following in respect of the priority claim(s) made in the international application.

1.  **Correction of priority claim.** In accordance with the applicant's notice received on: 21 July 1999 (21.07.99), the following priority claim has been corrected to read as follows:  
US 17 July 1998 (17.07.98) 60/093149
  - even though the indication of the number of the earlier application is missing.
  - even though the following indication in the priority claim is not the same as the corresponding indication appearing in the priority document:
2.  **Addition of priority claim.** In accordance with the applicant's notice received on: , the following priority claim has been added:
  - even though the indication of the number of the earlier application is missing.
  - even though the following indication in the priority claim is not the same as the corresponding indication appearing in the priority document:
3.  As a result of the correction and/or addition of (a) priority claim(s) under items 1 and/or 2, the (earliest) priority date is:
4.  **Priority claim considered not to have been made.**
  - The applicant failed to respond to the invitation under Rule 26bis.2(a) (Form PCT/IB/316) within the prescribed time limit.
  - The applicant's notice was received after the expiration of the prescribed time limit under Rule 26bis.1(a).
  - The applicant's notice failed to correct the priority claim so as to comply with the requirements of Rule 4.10.

The applicant may, before the technical preparations for international publication have been completed and subject to the payment of a fee, request the International Bureau to publish, together with the international application, information concerning the priority claim. See Rule 26bis.2(c) and the PCT Applicant's Guide, Volume I, Annex B2(1B).
5.  In case where multiple priorities have been claimed, the above item(s) relate to the following priority claim(s):
 

US 17 July 1998 (17.07.98) 60/093149
6. A copy of this notification has been sent to the receiving Office and
  - to the International Searching Authority (where the international search report has not yet been issued).
  - the designated Offices (which have already been notified of the receipt of the record copy).

The International Bureau of WIPO  
34, chemin des Colombettes  
1211 Geneva 20, Switzerland  
Facsimile No. (41-22) 740.14.35

Authorized officer  
R. Chrem  
Telephone No. (41-22) 338.83.38

## PATENT COOPERATION TREATY

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REC'D 04 OCT 2000  
WIPO PCT

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT  
(PCT Article 36 and Rule 70)

Applicant's or agent's file reference <b>P004733WOCTH</b>	<b>FOR FURTHER ACTION</b> <span style="float: right;">See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)</span>	
International application No. <b>PCT/GB99/01607</b>	International filing date (day/month/year) <b>21/05/1999</b>	Priority date (day/month/year) <b>22/05/1998</b>
International Patent Classification (IPC) or national classification and IPC <b>C12N15/86</b>		
Applicant <b>OXFORD BIOMEDICA (UK) LIMITED et al.</b>		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of 3 sheets.

3. This report contains indications relating to the following items:

- I  Basis of the report
- II  Priority
- III  Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV  Lack of unity of invention
- V  Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI  Certain documents cited
- VII  Certain defects in the international application
- VIII  Certain observations on the international application

Date of submission of the demand <b>09/12/1999</b>	Date of completion of this report <b>29.02.00</b>
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer  Huber, A  Telephone No. +49 89 2399 8173



**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT**

International application No. PCT/GB99/01607

**I. Basis of the report**

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

**Description, pages:**

1-46 as originally filed

**Claims, No.:**

1-20 as received on 23/08/2000 with letter of 21/08/2000

**Drawings, sheets:**

1/6-6/6 as originally filed

2. The amendments have resulted in the cancellation of:

the description, pages:  
 the claims, Nos.:  
 the drawings, sheets:

3.  This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

**see separate sheet**

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT**

International application No. PCT/GB99/01607

**V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

**1. Statement**

Novelty (N)	Yes: Claims 5-7, 11-16
	No: Claims 1-4, 8-10, 17-20
Inventive step (IS)	Yes: Claims 5
	No: Claims 6, 7, 11-16
Industrial applicability (IA)	Yes: Claims 1-20
	No: Claims

**2. Citations and explanations**

**see separate sheet**

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/GB99/01607

**Re Item I**

**Basis of the report**

Sequence listing pages 1-4 filed with the letter of 16.09.99 do not form part of the application (Rule 13<sup>ter</sup>.1(f) PCT).

**Re Item V**

**Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. The present application relates to retroviral delivery systems (vectors) in which the env region of the retrovirus has been replaced by a region coding for at least part of a rabies G protein.
2. Reference is made to the following documents:
  - D1: Reiser et al., Cold Spring Harbour, Abstract of paper presented at the 1997 meeting: Vector targeting strategies for therapeutic gene delivery, March 14-16, 1997 "High-titer pseudotyped HIV-1 vectors"
  - D2: WO 98 05759 A (UNIV CALIFORNIA (US)) 12 February 1998 (1998-02-12) cited in the application
  - D3: WO 95 22617 A (UNIV PARIS CURIE ;KLATZMANN DAVID (FR); SALZMANN JEAN LOUP (FR)) 24 August 1995 (1995-08-24)
3. Novelty and inventive step (Art. 33(2) and (3) PCT):
  - 3.1 The conference report of Reiser et al. (D1) which was kindly provided by the applicant, discloses a three-plasmid expression system used to generate HIV-1

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/GB99/01607

particles pseudotyped with VSV-glycoprotein. In addition, rabies G protein has been demonstrated to lead to the formation of HIV pseudotypes, albeit at lower titers ("the titers obtained so far are below the ones obtained with the VSV-G protein"). This does, however, not mean that the pseudotyped HIV-1 vector is not capable of transducing cells. It should also be noted that high virus titers may be desirable but are not required by the claims. There is no indication in D1 that the titer obtained may not be sufficient to be suitable for transducing cells.

In the opinion of the IPEA, the statement in D1 "using the improved vector system, post-mitotic rat cerebellar granule cells were transduced successfully using ShlacZ reporter constructs", cannot be interpreted in the way done by the applicant, namely that HIV pseudotyped with rabies G protein is not capable of transducing a target site. The "improved vector system" of Reiser et al. comprises a defective packaging construct, a plasmid encoding a heterologous env protein and a vector construct harboring a reporter gene such, e.g. ShlacZ.

Successful transduction was obtained with the complete vector system, i.e. not only the reporter gene was transduced. The conclusion drawn by the applicant that D1 implies that a target site was not successfully transduced with low titre HIV pseudotypes is therefore not accepted.

The newly introduced term "selectively" is not considered suitable to render the retroviral delivery system of Claim 1 novel over the system of D1. The HIV-1/rabies G protein pseudotypes of D1 are structurally indistinguishable from the retroviral delivery system of Claim 1. The capability of selectively transducing a target site is an inherent property of retroviruses pseudotyped with rabies G protein.

The subject-matter of Claims 1-4, 8-10 and 17-20 is therefore not considered novel in view of D1 (Art. 33(2) PCT).

3.2 The remaining claims are novel in view of D1, but are considered to lack the required inventive step (Art. 33(3) PCT).

In D1 it has already been shown that HIV can be successfully pseudotyped with the rabies env protein. The design of targetable vectors with cell-specific and organ-specific tropisms is proposed.

Generally, replacement of the retroviral env gene with a heterologous env gene ("pseudotyping") is widely known from the prior art and its advantage in

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/GB99/01607

broadening the infectious spectrum of the retroviral vectors and in the production of higher titres of the retroviral vectors has been recognized.

D2, for example, discloses the preparation of packaging cells for pseudotyping retroviral vectors.

Pseudotyped retroviral particles are produced by introducing a defective recombinant retroviral genome containing a NOI into a packaging cell line that contains nucleotide sequences coding for retroviral proteins for which the introduced retroviral genome is defective (gag, pol) and an inducible expression system that facilitated expression of a desired envelope protein. In a preferred embodiment, the nucleotide sequence encoding the envelope protein is derived from a rhabdovirus G protein, such as VSV. On page 11, lines 13-16, also rabies G protein is mentioned as choice to form pseudotyped retroviral virions.

Similarly, also D3 discloses a pseudotyped retroviral vector for transducing a NOI into a target cell, wherein the retroviral env gene is replaced by a heterologous env gene, for example the env gene of rabies virus (see claims 1 and 8).

Thus, having regard to D1 in combination with D2 and/or D3 the skilled person would be motivated to introduce a NOI into the pseudotyped retrovirus of D1. In the light of the prior art, it would also be obvious to use the pseudotyped retrovirus of D1 in medicine, resp. in the manufacture of a pharmaceutical composition to deliver a NOI to a target site and for affecting the infectious profile, the host range and/or cell tropism.

Consequently, the subject-matter of Claims 6, 7 and 11-16 does not involve the required inventive step.

3.3 Claim 5 is directed to a retroviral delivery system wherein the retroviral sequences are derived from the lentivirus EIAV. Since there is no suggestion found in the prior art which would prompt the skilled person to prepare pseudotyped EIAV-vectors instead of HIV-vectors, an inventive step can be acknowledged for the subject-matter of Claim 5.

T/N

## PATENT COOPERATION TREATY

09/701014

## PCT

## INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference <b>P004733WOCTH</b>	<b>FOR FURTHER ACTION</b> see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, Item 5 below.	
International application No. <b>PCT/GB 99/01607</b>	International filing date (day/month/year) <b>21/05/1999</b>	(Earliest) Priority Date (day/month/year) <b>22/05/1998</b>
Applicant <b>OXFORD BIOMEDICA (UK) LIMITED et al.</b>		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 3 sheets.

It is also accompanied by a copy of each prior art document cited in this report.

**1. Basis of the report**

a. With regard to the language, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of the sequence listing :

contained in the international application in written form.

filed together with the international application in computer readable form.

furnished subsequently to this Authority in written form.

furnished subsequently to this Authority in computer readable form.

the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2.  Certain claims were found unsearchable (See Box I).

3.  Unity of invention is lacking (see Box II).

4. With regard to the title,

the text is approved as submitted by the applicant.

the text has been established by this Authority to read as follows:

**RETROVIRAL DELIVERY SYSTEM**

5. With regard to the abstract,

the text is approved as submitted by the applicant.

the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the drawings to be published with the abstract is Figure No.

as suggested by the applicant.

because the applicant failed to suggest a figure.

because this figure better characterizes the invention.

3

None of the figures.

## INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 99/01607

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C12N15/86 C12N15/62 C12N7/01 C07K14/16 A61K48/00

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C12N C07K A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 93 01833 A (COMMW SCIENT IND RES ORG) 4 February 1993 (1993-02-04) the whole document	16, 17
Y	WO 94 08022 A (COMMW SCIENT IND RES ORG ;WALKER PETER JOHN (AU); PREHAUD CHRISTOP) 14 April 1994 (1994-04-14) page 10, line 35 -page 12, line 6 page 16, line 4 - line 17	1-15, 18-23
Y	WO 98 05759 A (HOPE CITY ;UNIV CALIFORNIA (US)) 12 February 1998 (1998-02-12) cited in the application page 11, line 13 - line 15; claims 1-24	1-15, 18-23
		-/-

 Further documents are listed in the continuation of box C. Patent family members are listed in annex.

## \* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the International filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the International filing date but later than the priority date claimed

"T" later document published after the International filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the International search

Date of mailing of the International search report

18 November 1999

03/12/1999

## Name and mailing address of the ISA

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NL - 2280 HV Rijswijk  
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
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## Authorized officer

Hornig, H

## INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 99/01607

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 95 22617 A (UNIV PARIS CURIE ;KLATZMANN DAVID (FR); SALZMANN JEAN LOUP (FR)) 24 August 1995 (1995-08-24) page 13, line 30 - line 36 page 21, line 3 - line 8 _____	1-15, 18-23
Y	WO 92 14829 A (UNIV CALIFORNIA ;VIAGENE INC (US)) 3 September 1992 (1992-09-03) the whole document _____	1-15, 18-23
A	P- COULON ET AL.: "An avirulent mutant of rabies virus is unable to infect motoneurons in vivo and in vitro" J. VIROLOGY, vol. 72, no. 1, January 1998 (1998-01), pages 273-278, XP002123083 AM.SOC.MICROBIOL., WASHINGTON,US cited in the application the whole document _____	1-23
A	EP 0 261 940 A (APPLIED BIOTECHNOLOGY INC) 30 March 1988 (1988-03-30) the whole document _____	1-23
A	WO 92 03537 A (THERION BIOLOG CORP) 5 March 1992 (1992-03-05) claims 1-43 _____	1-23
A	WO 96 09400 A (SYSTEMIX INC ;UNIV LELAND STANFORD JUNIOR (US)) 28 March 1996 (1996-03-28) cited in the application the whole document _____	1-23
A	WO 93 14188 A (UNIV MICHIGAN) 22 July 1993 (1993-07-22) the whole document _____	1-23

**INTERNATIONAL SEARCH REPORT**

Information on patent family members

International Application No

PCT/GB 99/01607

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9301833 A	04-02-1993	CA 2113572 A EP 0595970 A JP 6509228 T NZ 243611 A	04-02-1993 11-05-1994 20-10-1994 23-12-1993
WO 9408022 A	14-04-1994	AU 5103893 A EP 0672153 A JP 8501453 T ZA 9307164 A	26-04-1994 20-09-1995 20-02-1996 23-05-1994
WO 9805759 A	12-02-1998	US 5739018 A	14-04-1998
WO 9522617 A	24-08-1995	FR 2716461 A FR 2716459 A AT 172496 T AU 1851895 A CA 2183151 A DE 69505493 D DE 69505493 T EP 0738327 A EP 0855185 A ES 2124532 T FI 963246 A JP 9509060 T NO 963358 A US 5948675 A ZA 9501451 A	25-08-1995 25-08-1995 15-11-1998 04-09-1995 24-08-1995 26-11-1998 22-04-1999 23-10-1996 29-07-1998 01-02-1999 16-10-1995 16-09-1997 02-09-1996 07-09-1999 18-12-1995
WO 9214829 A	03-09-1992	AU 663470 B AU 8430291 A CA 2104396 A EP 0572401 A JP 6504905 T US 5512421 A US 5817491 A US 5670354 A	12-10-1995 15-09-1992 20-08-1992 08-12-1993 09-06-1994 30-04-1996 06-10-1998 23-09-1997
EP 0261940 A	30-03-1988	CA 1312837 A JP 63245670 A US 5242829 A	19-01-1993 12-10-1988 07-09-1993
WO 9203537 A	05-03-1992	AT 163047 T CA 2089497 A DE 69128898 D DE 69128898 T EP 0652967 A JP 6500232 T US 5420026 A US 5858726 A	15-02-1998 16-02-1992 12-03-1998 28-05-1998 17-05-1995 13-01-1994 30-05-1995 12-01-1999
WO 9609400 A	28-03-1996	AU 3635695 A	09-04-1996
WO 9314188 A	22-07-1993	AU 3434393 A	03-08-1993